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A Two Dose Combined Hepatitis A and B Vaccine in Chinese Youngsters

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This open, randomized study was conducted in healthy Chinese youngsters, aged between 10 and 19 years to compare the reactogenicity and immunogenicity of two vaccines: the combined vaccine against hepatitis A and B was administered in a two-dose schedule with the profile of the corresponding monovalent vaccines, while the concomitant vaccine was administered also on a two-dose schedule but simultaneously in opposite arms. All vaccinees had antibodies against hepatitis A (anti-HAV) after the 2-dose administration, whereas all but four in the first and two in the second group had protective titres against hepatitis B (anti-HBs). At month 7, the geometric mean titres for both antibodies were more than double for the group of subjects receiving the combined vaccine: 3,701 vs. 1,705 mIU/ml for the anti-HAV, and 1,524 vs. 720 mIU/ml for the anti-HBs response. Injection site pain was the most commonly reported local symptom and headache was the most reported general symptom. It is concluded that this combined vaccine against hepatitis A and B, administered according to a two-dose schedule, is well-tolerated and highly immunogenic. ***J. Med. Virol. 59:1–4, 1999.***

KEY WORDS: hepatitis A; hepatitis B; vaccine; immunogenicity; combined vaccine

INTRODUCTION

Hepatitis A and B constitute a major public health problem world-wide. Approximately 1.4 million cases of hepatitis A virus (HAV) infections are reported every year and the true incidence may be much higher [Hadler, 1991]. The hepatitis B virus (HBV) resides in a reservoir of between 300 and 350 million chronic carriers. As many of 30% of these carriers are expected to die of the sequelae of chronic infection: chronic liver disease, cirrhosis, and ultimately hepatocellular carcinoma [Maynard et al., 1989].

HAV is a food- and water-borne virus, transmitted mainly through a feacal/oral route and direct person-to-person contact. Different patterns of HAV antibody prevalence have been described, with variations reflecting the level of economic development [Hadler, 1991]. In areas of high endemicity, 90% of the children are infected by the age of 10. Infection is largely asymptomatic and hepatitis A is not a clinical problem [Gust, 1992]. In areas of intermediate endemicity, 90% seroprevalence is not reached until early adulthood. In developed countries, endemicity is low. A high prevalence of antibodies is found only in older cohorts possibly reflecting historical exposure. These patterns may vary within countries. In countries or regions with lower endemicity hepatitis A outbreaks can be frequent [Hadler, 1991]. HAV infection in patients with chronic liver disease can have serious consequences [Lee et al., 1997; Keefe et al., 1998]. Vaccines against hepatitis A are safe and highly immunogenic both in healthy subjects and in patients with chronic liver disease [Lee et al., 1997, 1993].

Control and prevention of HBV infection has been recognized world-wide as an important public health issue. In areas of high endemicity, the majority of infections with HBV occur perinatally or during early childhood [Maynard, 1990]. Since there is currently no specific treatment for the disease, vaccination is the best and most practical tool to prevent disease and reduce chronic carriage. Both plasma-derived and recombinant hepatitis B vaccines are safe and highly immunogenic, both in clinical trials and in extensive post-licensing follow-up [Lo et al., 1985, 1988; Poovorawan et al., 1989].

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Recently, a combined hepatitis A and hepatitis B vaccine has been developed to administer on schedule of 0, 1, and 6 months. This combined vaccine (Twinrix, SmithKline Beecham Biologicals, Rixensart, Belgium) is well-tolerated and induces a high immunogenic response similar in effect to the respective monovalent vaccines [Bruguera et al., 1996; Leroux-Roels et al., 1996]. It can reduce the number of vaccine doses needed to obtain protection against multiple disease and offers more convenience to the vaccinees. An additional reduction in doses would further improve compliance and convenience. An earlier study demonstrated an excellent immunological response elicited by hepatitis A vaccine administered in a single primary dose, followed by a second dose at month 6 [Lee et al., 1996].

The feasibility of a combined high dose hepatitis A and B vaccine administered in a single primary dose followed by a second one at month 6 was evaluated to provide long-term immunity and protection. Its immunogenicity and reactogenicity was compared with that of the corresponding monovalent vaccines administered simultaneously in opposite arms.

MATERIALS AND METHODS

Study Participants and Inclusion/ Exclusion Criteria

One hundred three healthy Chinese youngsters were enrolled for this trial after written informed consent was obtained. The study protocol was approved by the Ethics Committees of the Veterans General Hospital-Taipei, and the Department of Health, Executive Yuan, Republic of China. Subjects were excluded from the study if they had antibodies to HAV (anti-HAV), hepatitis B surface antigen (HBsAg), antibodies to HBsAg (anti-HBs), or antibodies to hepatitis B core antigen (anti-HBc) and abnormal liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT) above two-fold the upper normal laboratory value]. The inclusion criteria specified that adolescents between 11 and 19 years of age were to be enrolled for the study. However, 9 subjects (4 in group 1 and 5 in group 2) were 10 years old and were not eliminated from the study.

Study Design and Vaccines

The 103 subjects were allocated randomly to two study groups. The first group received the combined high dose hepatitis A and B vaccine and the second group received simultaneously a hepatitis A vaccine in one arm and a hepatitis B vaccine in the opposite arm. Both groups received the vaccines on a two dose schedule of 0 and 6 months. The high dose vaccine contained at least 720 ELISA units (EL.U) of inactivated hepatitis A (strain HM 175 RIT 4380) and 20 μg of recombinant HBsAg and was administered in a 0.5 ml dose. The monovalent hepatitis A vaccine contained at least 720 EL.U of inactivated HAV in a 0.5 ml dose. The monovalent hepatitis B vaccine contained 20 μg of recombinant HBsAg in a 0.5 ml dose. All antigens were adsorbed onto aluminum. Blood samples were obtained from the vaccinees at screening, months 1, 2, 6, and 7.

To assess reactogenicity, every subject was asked to complete a diary card after every vaccine administration. Solicited local symptoms consisted of injection site soreness, swelling or redness, whereas solicited general symptoms included fatigue, headache, fever, nausea, vomiting, and malaise. Solicited symptoms were recorded in the evening following vaccine administration and for 3 consecutive days. Unsolicited adverse reactions were recorded within 30 days following each dose of vaccine and serious adverse reactions were recorded throughout the study. Maximum intensity of the symptoms was scored according to one of the following categories: grade 1 symptoms are easily tolerated, grade 2 symptoms are sufficiently discomforting to interfere with daily activities, and grade 3 symptoms are preventing normal activities, local swelling and redness >30 mm and persisting >24 hours, or fever over 39°C.

Laboratory Analysis

At screening, serum liver enzymes (ALT and AST) were measured. Anti-HAV antibodies were also measured using a radioimmunoassay (RIA) kit (HAVAB®, Abbott Laboratories, Chicago, Ill., USA) and thereafter with enzyme immunoassay kit (Enzymun-Boehringher kit, Mannheim, Germany). HBsAg, anti-HBc, and anti-HBs antibodies were measured using RIA kits (AUSRIA II®, CORAB®, and AUSAB®, Abbott Laboratories, Chicago, IL). Serum liver enzymes were measured by a photoelectric colourimeter (Sigma Diagnostics Transaminase, St. Louis, MO). Upper normal limits were taken as 35 SF U/ml for ALT and 40 SF U/ml for AST. Serum samples taken at months 1, 2, 6 and 7 were tested in SmithKline Beecham Biologicals' laboratories for anti-HAV (Enzymun test) and anti-HBs antibodies titres (AUSAB®). Seropositivity was defined as the appearance of antibodies ≥1 mIU/ml for anti-HBs antibodies and ≥33 mIU/ml for anti-HAV antibodies. Seroprotection rate was defined, for anti-HBs antibodies, as the percentage of subjects with titres ≥ 10 mIU/ml. The geometric mean titres (GMT) were calculated using the log-transformation of seropositive titres (≥ 33 mIU/ml for anti-HAV and ≥ 1 mIU/ml for anti-

TABLE I. Demographics of Vaccinees Who Received Combined or Concomitant Hepatitis A and B Vaccines Administration

Group[a]	Gender	n	Mean age (years)	Range	SD[b]
Combined	Female	24	14.2	10–19	2.90
	Male	27	14.0	10–17	2.53
	Total	51	14.1	10–19	2.68
Concomitant	Female	19	12.1	10–18	1.79
	Male	33	12.5	10–19	2.43
	Total	52	12.4	10–19	2.21

[a]Combined, the group received the combined vaccine; concomitant, the group receiving the vaccines in opposite arm.
[b]SD, standard deviationa.

TABLE II. Immune Response of Vaccinees Who Received Combined or Concomitant Hepatitis A and B Vaccines Administration*

Immune response	Group	Month of testing	% of sero-positive	% of sero-protective[a]	GMT[b] (mIU/ml)	95% CI[c]
Anti-HAV	Combined	1	98.0		379	277–519
	(n = 49)	2	95.9		210	162–273
		6	85.7		122	92–160
		7	100		3701	2,959–4,630
	Concomitant	1	97.9		219	168–287
	(n = 47)	2	91.5		136	109–168
		6	85.1		74	60–92
		7	100		1705	1,343–2,165
Anti-HBs	Combined	1	61.2	51.0	55	24–127
	(n = 49)	2	73.5	40.8	19	9–42
		6	79.6	51.0	17	8–33
		7	93.9	91.8	1524	844–2,752
	Concomitant	1	70.2	48.9	36	17–78
	(n = 47)	2	70.2	42.6	23	12–43
		6	72.3	42.6	15	8–28
		7	95.7	95.7	720	356–1,457

*Vaccines were given at month 0 and 6.
[a]Anti-HBs titre ≥10 mIU/ml.
[b]GMT, geometric mean titre.
[c]CI, confidence intervals.

TABLE III. Incidence of Solicited Local and General Symptoms in Vaccinees Who Received Combined or Concomitant Hepatitis A and B Vaccines Administration*

			Local			General		
Dose	Group	n[a]	Redness	Soreness	Swelling	Fatigue	Headache	Fever
1	Combined	50	2.0	16.0	2.0	6.0	8.0	2.0
	Concomitant	49				6.1	2.0	0
	HA vaccine[b]		0	8.2	0			
	HB vaccine[c]		0	22.4	0			
2	Combined	50	0	18.0	0	4.0	6.0	2.0
	Concomitant	49				8.2	2.0	0
	HA vaccine		0	8.2	0			
	HB vaccine		0	32.7	0			
1 + 2	Combined	100	1.0	17.0	1.0	5.0	7.0	2.0
	Concomitant	98				7.1	2.0	0
	HA vaccine		0	8.2	0			
	HB vaccine		0	27.6	0			

*All data are in %.
[a]n = total number of symptom sheets returned.
[b]HA vaccine, hepatitis A vaccine.
[c]HB vaccine, hepatitis B vaccine.

HBs) and taking the anti-log of the mean of these transformed values.

Statistical Analysis

The study was not statistically powerful enough and therefore only a descriptive analysis with 95% confidence intervals for immunogenicity was performed.

RESULTS

Demographics and Study Compliance

One hundred three volunteers were enrolled for the study. Four subjects were eliminated from the overall analysis of reactogenicity (one in group 1 and 3 in group 2). A further four were excluded from the overall analysis of immunogenicity because of non-compliance with the protocol. None were dropped out because of adverse events. Demographic characteristics are shown in Table I. There were no statistically significant differences between the two study groups in sense of mean ages, female/male ratio and gender.

Immunogenicity of the Vaccine

Hepatitis A response. At month 1, all but one subject in each group seroconverted after a single dose of vaccine (Table II). Just prior to the second dose, 85.7% in group 1 and 85.1% in group 2 had detectable anti-HAV. After the second dose, all subjects in both groups were sero-positive for anti-HAV but the GMT levels in the group receiving the combined hepatitis A and B vaccine were more than double.

Hepatitis B response. At month 1, approximately two in three vaccines had detectable anti-HBs (Table II). Half of the vaccinees had protective antibody levels. Just prior to the second dose, seropositivity had increased and sero-protection rates maintained in both

groups. The GMTs of anti-HBs had decreased. After the second dose, nearly all vaccinees in both groups became seropositive. Four subjects in the first group and two in the second group did not have protective titres above 10 mIU/ml. The GMT of anti-HBs was approximately two times higher in the group receiving the combined vaccine.

Reactogenicity Analysis

The occurrence and intensity of solicited and unsolicited local and general symptoms were recorded on the day of vaccination and the three subsequent days (Table III). The nature of symptoms was more local than general in both vaccination groups. Soreness was the most frequently reported local symptom in both groups but this was only once scored grade 3 by a subject in group 2. No other local symptoms were scored grade 3. Following vaccination, fatigue and headache were the most frequently reported general symptoms. After the second dose, one subject reported fatigue as scored grade 3. There were no incidences of malaise, nausea or vomiting following any of the doses. All symptoms resolved during the 4-day follow-up. No unsolicited symptoms or serious adverse events were reported.

DISCUSSION

The aim of the study was to compare the reactogenicity and immunogenicity of a combined vaccine against hepatitis A and B administered on a two-dose schedule with the profile of the corresponding monovalent vaccines also administered on a two-dose schedule, but simultaneously in opposite arms.

After two doses of vaccine in both groups, all subjects had antibodies against hepatitis A, and all but four in the combined group and two in the group receiving the monovalent vaccines had protective levels against hepatitis B. These rates are similar to the rates observed with the licensed combined vaccine [Ambrosh et al., 1992; Kallinowski et al., 1996] that is administered on a three-dose schedule: a primary dose at month 0 and 1 followed by a third dose at month 6. For both antigens, the GMTs of respective antibody obtained in the group receiving the combined vaccine were more than double the GMTs for the groups receiving the monovalent vaccine. An explanation for these higher GMTs could be a possible synergistic improved immunogenicity of the combined vaccine, also observed by other investigators [Ambrosh et al., 1992; Reutter et al., 1998].

In both study groups, the vaccines were well tolerated and the reactogenicity profile was similar. The most frequent reported local symptom was injection site soreness, and headache was the most reported general symptom. Only five reported symptoms were scored as grade 3 but all symptoms resolved within the follow-up period of 4 days.

In conclusion, this combined vaccine against hepatitis A and B, administered on a two-dose schedule, is well tolerated and highly immunogenic. It offers the advantage of fewer injections with similar protection, more convenience to the vaccinees and less administration costs. A further reduction of the number of doses required makes these advantages even bigger.

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